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13. ABSTRACT (Maximum 200 Words)

This study investigates the carcinogenic and imunotoxic potential of embedded fragments of depleted uranium (DU) and a heavy-metal tungsten alloy (WA). Male Fischer 344 rats are surgically implanted with pellets of DU, WA, tantalum (inert metal, negative control), or nickel (known carcinogen, positive control). In Year 3 of this study, we found that implanted WA resulted in tumors at the implantation site in 100% of the rats. These tumors developed rapidly (within 18-22 weeks) after pellet implantation, exhibited extremely aggressive growth characteristics, and metastasized to the lung. The tumors were identified by histopathology and immunohistochemisty as high-grade pleomorphic rhabdomyosarcomas. In addition, rats in the high-dose WA group exhibited signs of polycythemia as early as one month after pellet implantation. Rats in the DU or tantalum groups showed no pellet-associated tumors for up to 2 years after implantation.

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INTRODUCTION

Advancement in weapons design has led to the introduction of several potentially toxic metals, such as depleted uranium (DU), onto the battlefield. The Persian Gulf War in 1991 saw the first combat use of DU kinetic penetrator munitions, and their success against enemy armor was dramatic. The demonstrated effectiveness of DU munitions in the first Gulf War has led other nations, some not friendly to the United States, to adopt these weapons into their own arsenals. Other types of kinetic energy penetrators use heavy-metal tungsten alloys (WA) in place of DU. In future conflicts, the United States will have to deal with an increased number of casualties from the use of these weapons. Because both DU- and WA-based munitions are relatively recent additions to the list of militarily relevant metals, little is known about the health effects of these metals after internalization as embedded shrapnel. This study was designed to assess the carcinogenic and immunotoxic potential of DU and WA using the Fisher 344 rat model and modified National Toxicology Program protocols for such studies. Responses to the test metals are being compared to responses to tantalum, a biologically inert metal that serves as a negative control and nickel, a known heavy-metal toxin and carcinogen that serves as a positive control. This research addresses the DOD effort to understand the potential health risks associated with DU and WA exposure in order to develop appropriate medical treatment protocols for personnel wounded by fragments of these metals.

BODY

Statement of Work

This four-year study is an assessment of the immunotoxic and carcinogenic potential of embedded fragments of DU and WA in laboratory rats. Responses to these metals are compared to the biologically inert metal, tantalum, and the carcinogen and heavy-metal toxin, nickel. For these experiments, rats are implanted with tantalum pellets alone (metal control group), a mixture of DU and tantalum pellets (low DU group), DU pellets alone (high DU group), a mixture of WA and tantalum pellets (low WA group), or WA pellets alone (high WA group). There is also a non-surgical control group and a positive carcinogenesis control group implanted with nickel pellets. Animals will be euthanized and various analyses performed 1, 3, 6, 12, 18, and 24 months after implantation. Analyses include histopathological examination and metal determinations as well as assessments of mutagenicity and cytogenicity. A battery of immunological tests designed to assess both humoral and cell-mediated immunity, as well as the innate immune response, will be conducted at 1, 3, 6, and 12 months.

Progress to Date

Because of the unexpected finding of rapid tumor formation in WA-implanted rats (reported in our Year 2 Annual Report), we were forced to deviate from our original pellet implantation and euthanasia schedule. As a result, some analyses and data compilation, previously scheduled to be completed in Year 3, are not yet finished. However, rodent implantation surgery and euthanasia that were originally scheduled for Year 4 have already been conducted. At this time, implantation surgery and euthanasia of all experimental groups (1-, 3-, 6-, 12-, 18-, and 24-month) are complete. A revised timeline for the remaining Year 4 work is presented below, as are detailed results corresponding to the various project tasks.

Year 4 Revised Work Schedule

- Complete cytogenetic analyses
- Complete metal measurements
- Analyze and compile all data
- Provide final report

Task 1 - *Determine whether embedded fragments of DU or WA cause cancer in rodents.*

No tumors, resulting from pellet implantation, were observed in the tantalum, low DU, or high DU groups at the 1-, 3-, 6-, 12-, 18-, or 24-month time points. Gross necropsies of these groups revealed no abnormalities. The 18- and 24-month animals, in all surviving groups, exhibited health problems associated with old age (e.g., testicular cancer, benign abdominal growths, etc.). These health problems were not associated with a particular treatment group. They were found across all experimental groups. As a result of these age-related health problems, many of the 18- and 24-month animals were euthanized before reaching their experimental endpoint; however, no abnormalities

associated with the tantalum or DU implanted pellets were observed. Approximately 70% of the rodents reached the 18-month experimental endpoint. Only one rodent (a high-dose DU rat) reached the 24-month experimental timepoint. A table showing survival data for all experimental groups is found in the Appendices (Table 1).

While all the rodents in the non-surgical, tantalum, and DU groups either reached their experimental endpoint or were euthanized due to age-related maladies, the same cannot be said for the WA and nickel groups. By 14-18 weeks after implantation, many of the animals began to develop palpable tumors at the pellet implantation sites. All animals in the low-dose WA, high-dose WA, and nickel groups eventually developed tumors and were euthanized. Criteria for euthanasia is based upon previously published standards (Tomasovic et al., 1988). The high-dose WA group survived the shortest time, with the nickel and low-dose WA groups only slightly longer. Upon euthanasia, the pellets were removed and showed apparent oxidation, but had lost only about 5 % of their mass during implantation. Gross necropsies showed tumors surrounding the WA or nickel pellets. The tumor appeared to displace and replace the skeletal muscle surrounding the pellet. Metastases were invariably found in the lungs of both the low and high WA groups with additional growths occasionally found in the abdominal cavity.

In many cases the leg tumors would undergo rapid aggressive growth, more than doubling their size in a matter of days. Histopathological analysis revealed the presence of pleomorphic neoplastic cells with no bone or smooth muscle involvement. Immunohistochemical analysis was positive for desmin and negative for smooth muscle actin, indicating the tumor is most likely a rhabdomyosarcoma. No other apparent tissue abnormalities were observed. Histopathological analysis will be completed in Year 4.

General health parameters

Change in body weight is considered one of the sensitive, early indicators of change in overall health. The animals in this study were weighed weekly. Graphs showing body weight gain over time for all of the experimental groups are shown in Figures 1-6 in the Appendices. Error bars have been omitted for the sake of clarity. In the week immediately after pellet implantation, there is no or only a very slight gain in body weight as the animals recover from surgery. After this recovery period, animals in all groups gain weight at a consistent rate for the next month. After that time, rodents in the high-dose DU group gain weight at a slower rate than the other experimental groups. This decreased rate of body weight gain continues throughout the lifespan of the rat. A similar effect for DU was reported previously for Sprague-Dawley rats (Pellmar et al., 1999). The spikes seen in the WA groups near the end of their lifespan can be attributed to the low number of animals (one animal in each case) surviving to that point.

Hematological and serum clinical chemistry data for all experimental groups are shown in Tables 2-13 and 14-19, respectively, in the Appendices. Several results are noteworthy. Rats implanted with 20 WA pellets exhibited significant increases in white blood cell counts, red blood cell counts, hemoglobin, and hematocrit levels compared to control rats, while rats implanted with 20 Ni pellets had significant decreases in red blood cell counts, hemoglobin, and hematocrit levels. Hematological parameters from low-dose WA rats were not statistically different from controls. The hematological changes observed in the high-dose WA rats are suggestive of polycythemia. Cobalt has been used experimentally to induce polycythemia in rats (Rakusan et al., 2001; Endoh et al., 2000)

although the concentration required is far greater than the amount that could be provided by the WA pellets. The speed at which these hematological changes occurred in the high-dose WA rats was also surprising. Statistically significant increases in red blood counts, hemoglobin, and hematocrit levels were observed in high-dose WA animals as early as one month after pellet implantation and persisted throughout the experimental period. In addition, there were statistically significant increases in the numbers of neutrophils, lymphocytes, monocytes, and eosinophils present in high-dose WA animals. Low-dose WA animals had elevated neutrophil, lymphocyte, and monocyte counts, but only the neutrophil counts were statistically different from the controls. The Ni-implanted animals had significantly lower lymphocyte counts than the controls. All other parameters were statistically identical to the controls. These results suggest a dose-dependent perturbation in many hematology parameters as a result of an increasing WA pellet number.

Metal effects on specific organ systems can often be assessed by measuring organ/body weight ratios. Organ weights and organ/body weight ratios for all experimental groups are found in the Appendices (Tables 20-25). The organs assessed were spleen, thymus, liver, kidney, and testes. Organ weights are provided in the tables, although organ/body weight ratios give a more realistic assessment of organ toxicity. Low-dose DU animals showed an increased kidney/body weight ratio, compared to control, at 1 and 3 months post-implantation. However, by 6 months the ratio had returned to normal and remained there for the duration of the experiment. Surprisingly, the high-dose DU groups did not show these kidney changes, but did show decreases in liver/body weight ratios starting at 3 months post-implantation. These changes persisted throughout the duration of the experiment. The most remarkable changes were seen with the high-dose WA group. Starting at 1 month post-implantation, these animals had extremely elevated spleen/body weight ratios until they were euthanized at approximately 20-24 weeks. In addition, beginning at 3 months post-implantation, kidney/body weight ratios were also elevated.

Task 2 - *Measure tissue levels of DU or WA after chronic in vivo exposure.*

Analytical preparation of the several thousand tissue samples collected in this project is ongoing. We have been able to simultaneously measure the levels of tantalum, tungsten, nickel, cobalt, and uranium in a variety of tissues using inductively coupled plasma mass spectrometry (ICP-MS). Matrix effects, particularly in bone, liver, and kidney, have hindered our attempts to accurately assess the nickel and cobalt levels in these samples, but with recent analytical modifications we appear to have solved this dilemma. With the impending departure of our ICP-MS operator, we are currently training a replacement in order to continue with the analysis of the samples. The metal measurements will be completed in Year 4.

Task 3 - *Assess the genotoxicity and mutagenicity after chronic in vivo exposure to DU or WA.*

The number and types of chromosomal aberrations in blood lymphocytes as a result of exposure to embedded DU or WA are currently being assessed and will be completed in Year 4. The mutagenicity assessments of urine and serum samples from the 6- and 12-month animals have been completed. There was no indication that serum from

any of the experimental groups was mutagenic when assayed by the Ames bacterial reversion assay. However, urine from the high-DU and high-WA groups was significantly more mutagenic than urine from non-surgical or tantalum implanted rats (Appendices – Table 26). This result was not unexpected as one of the major routes of excretion of these metals from the body is in the urine. No urine was collected from the 18- and 24-month animals because, due to the declining health of the rodents, we opted against stressing the animals further by housing them in the metabolic cages required for urine collection. The serum samples from the 18- and 24-month animals are currently being analyzed for mutagenic activity.

Task 4 - *Determine the effect of embedded DU and WA on the organs of the immune system.*

The immune organ weights (spleen and thymus) and immune organ weight/body weight ratios have already been shown (Tables 20-22 of the Appendices). Splenocyte and thymocyte cellularities (number of cells/gram wet weight of tissue), as well as bone marrow cellularity (number of cells/femur) are shown for 1-, 3-, 6-, and 12-month animals in Tables 27-30 of the Appendices. Thymus and bone marrow cellularities appear to be affected more by DU exposure than by WA. Spleen cellularity is lower in both WA groups at 1 month post-implantation. Given the associated hematological and organ weight data, it appear that splenocytes from WA animals may be larger than normal. This finding awaits histopathological verification.

We are currently analyzing the data obtained by flow cytometric analysis of peripheral blood lymphocytes, splenocytes, and thymocytes in order to investigate any changes in the subpopulations of cells that comprise these immune system organs.

Task 5 – *Evaluate the effect chronic in vivo exposure to DU and WA has on immune function, including cell-mediated, humoral, and innate immunity.*

Three tests of immune function were conducted: the natural killer (NK) cell assay, the cytotoxic T-lymphocyte assay, and the antibody plaque-forming cell assay. Both low- and high-dose DU groups showed transient decreases in NK activity, the low-dose group at 1 month and the high-dose group at 3 months post-implantation. NK activity in both WA groups was lower than control groups at both the 1 and 3 month time period (Table 31, Appendices). Beyond 3 months, no activity was detectable in any of the experimental groups corroborating what has been reported in the literature.

Cytotoxic T-lymphocyte activity (Table 32, Appendices) was decreased at 6 months post-implantation in both DU groups, but returned to normal in both groups at 12 months post-implantation. Both WA groups also exhibited decreased cytotoxic T-lymphocyte activity at 6 month post-implantation, with the high-dose WA rats also showing decreased activity at 3 months. Because aggressive tumor formation surrounding the WA pellets required euthanasia of the rodents, no 12-month data was obtained.

The antibody plaque-forming cell (APC) assay is a measure of the ability of the animal to recognize injected sheep red blood cells as foreign, present the antigen to the appropriate cells, and make antibodies against it. The assay requires the proper functioning and interaction of macrophages, T-cells, and B-cells and, as such, is considered a sensitive indicator of the overall functioning of the immune system. The

data in Table 33 of the Appendices show that low-dose DU rats showed lower APC activity (expressed as number of plaques/spleen) at all times tested. The high-dose DU groups were not different from control at 1 and 3 months post-implantation. However, at 6 months activity was lower than control. Activity was also slightly lower, though not statistically significant, at 12 months post-implantation. Both WA groups were no different than control at 1 month post-implantation. Activity then decreased at 3 months. Low-dose WA rats also exhibited decreased APC activity at 6 months post-implantation. Because of the condition of the high-dose WA rats, no APC determinations were obtained at 6 months post-implantation.

KEY RESEARCH ACCOMPLISHMENTS

- All rodents have been implanted and have reached their experimental endpoints.
- All animals implanted with WA (both low and high groups) or nickel developed tumors, identified as rhabdomyosarcomas, at the implantation site.
- Tumor development occurred most rapidly in the high WA group.
- Tumors metastasized to the lung in both the low and high WA groups.
- Rodents in the high WA group exhibited splenomegaly and hematological changes suggesting polycythemia.

REPORTABLE OUTCOMES

Oral presentation by Dr. David McClain at the US Army Heavy Metals Office Heavy Alloys Workshop, Stevens Institute of Technology, Hoboken, NJ, 10-11 Feb 2004. Title: Tumor Induction in Rats by Embedded Tungsten Alloy Fragments.

Oral presentation by Dr. David McClain at the United States/United Kingdom International Exchange Agreement 1443 Workshop (US/UK IEA 1443), US Army Research Laboratory, Aberdeen, MD, 24 June 2004. Title: Tumor Induction in Rats by Embedded Tungsten Alloy Fragments

Oral presentation by Dr. David McClain at the Armed Forces Radiobiology Research Institute Seminar Series, 5 March 2004. Title: Investigation of Tumor Induction in Rats by Embedded Tungsten Alloy Fragments.

Oral presentation by Dr. David McClain at the Armed Forces Radiobiology Research Institute Scientific Program Overview, AFRRI Board of Governors Meeting, 27 July 2004. Title: Investigation of Health Effects of Embedded Tungsten Alloy Fragments in Rats.

Oral presentation by Dr. John Kalinich at the Armed Forces Radiobiology Research Institute Seminar Series, March 19, 2004. Title: Immunotoxic Potential of Militarily Relevant Heavy Metals.

Manuscript submitted: John F. Kalinich, Christy A. Emond, Thomas K. Dalton, Steven R. Mog, Gary D. Coleman, Jessica E. Kordell, Alexandra C. Miller, and David E. McClain "Embedded weapons-grade tungsten alloy shrapnel rapidly induces rhabdomyosarcomas in rats"

CONCLUSIONS

The project continues ahead of schedule and no major experimental difficulties have been encountered. However, the unexpected finding of rapid and aggressive tumor development at the implantation sites in the WA groups raises some serious concerns. Heavy-metal tungsten alloys have been proposed as replacements for DU in armor penetrators. In fact, many countries, some unfriendly to the U.S., already possess tungsten munitions. As a result, future combat could produce large numbers of U.S. personnel with tungsten fragment injuries with military surgeons not having the best information available to deal with those injuries.

It was not surprising that the nickel-implanted animals developed tumors nor was the tumor type unexpected. Previous work has shown that intramuscular injections of insoluble nickel or cobalt result in tumor formation (mainly rhabdomyosarcomas) at the injection site (Shibata et al., 1989; Heath, 1956). What was surprising was the speed at which this occurred in the nickel-implanted animals. In the studies cited above, tumor development occurred approximately 50 weeks after injection. The fact that tumor development was much more rapid in the high WA group than in the nickel group suggests a synergistic or additive effect of the various components of the WA not active with nickel alone. Because of the lack of information on the health effects of embedded fragments of these types of mixtures, we recommend funding be made available for an additional study to investigate tumor development patterns for implanted tungsten and cobalt pellets alone, and possibly tungsten/cobalt and tungsten/nickel pellets, so that a comparison to WA and nickel can be made and the exposure risk put into perspective. In addition, a study following the National Toxicology Program guidelines should be funded investigating the carcinogenic potential of embedded tungsten alloy fragments in a second rodent species, such as the mouse.

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APPENDICES

Table 1. Survival Times of Pellet-Implanted Rodents

Time	Experimental Group	Mean (weeks) ± sem
24 Month	Non-Surgical	83.44 ± 2.05
(104 weeks)	Tantalum	82.69 ± 4.11
	DU-low	85.44 ± 2.82
	DU-high	81.69 ± 3.25
	WA-low	27.13 ± 1.06
	WA-high	21.75 ± 0.37
	Nickel	26.75 ± 0.59
18 Month	Non-Surgical	75.80 ± 1.20
(78 weeks)	Tantalum	74.00 ± 2.70
	DU-low	72.90 ± 2.46
	DU-high	74.30 ± 2.47
	WA-low	25.50 ± 1.83
	WA-high	20.90 ± 0.43
	Nickel	24.80 ± 0.36
12 Month	Non-Surgical	50.70 ± 0.91
(52 weeks)	Tantalum	52.00 ± 0.00
	DU-low	52.00 ± 0.00
	DU-high	52.00 ± 0.00
	WA-low	27.70 ± 0.97
	WA-high	22.25 ± 0.59
	Nickel	23.90 ± 0.31
6 Month	Non-Surgical	26.00 ± 0.00
(26 weeks)	Tantalum	26.00 ± 0.00
	DU-low	26.00 ± 0.00
	DU-high	26.00 ± 0.00
	WA-low	24.85 ± 0.52
	WA-high	22.40 ± 0.53
	Nickel	23.80 ± 0.55
3 Month	Non-Surgical	13.00 ± 0.00
(13 weeks)	Tantalum	13.00 ± 0.00
	DU-low	13.00 ± 0.00
	DU-high	13.00 ± 0.00
	WA-low	13.00 ± 0.00
	WA-high	13.00 ± 0.00
	Nickel	13.00 ± 0.00
1 Month	Non-Surgical	4.00 ± 0.00
(4 weeks)	Tantalum	4.00 ± 0.00
	DU-low	4.00 ± 0.00
	DU-high	4.00 ± 0.00
	WA-low	4.00 ± 0.00
	WA-high	4.00 ± 0.00

Figure 1

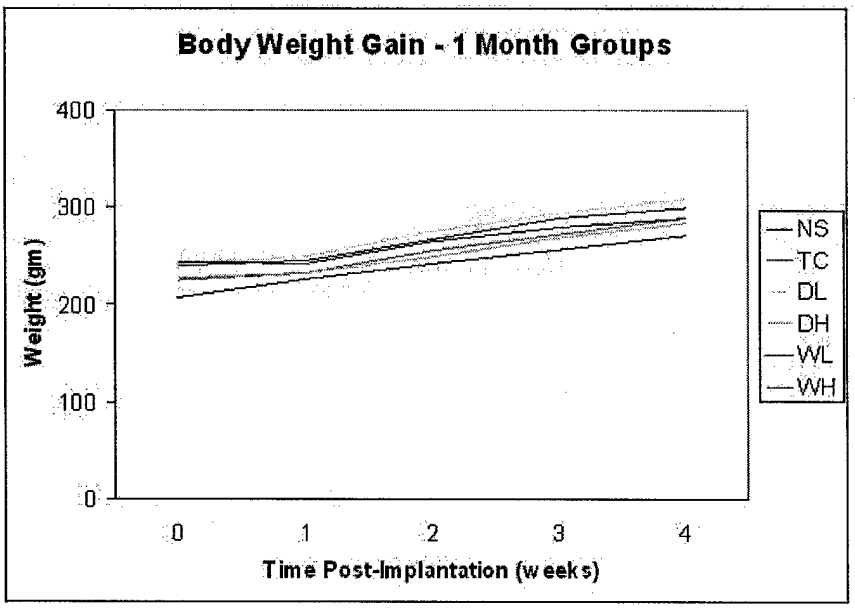

Body Weight Gain - 1 Month Groups
Weight (gm)
400
300
200
100
0
0
1
2
3
4
Time Post-Implantation (weeks)
NS
TC
DL
DH
WL
WH

Figure 2

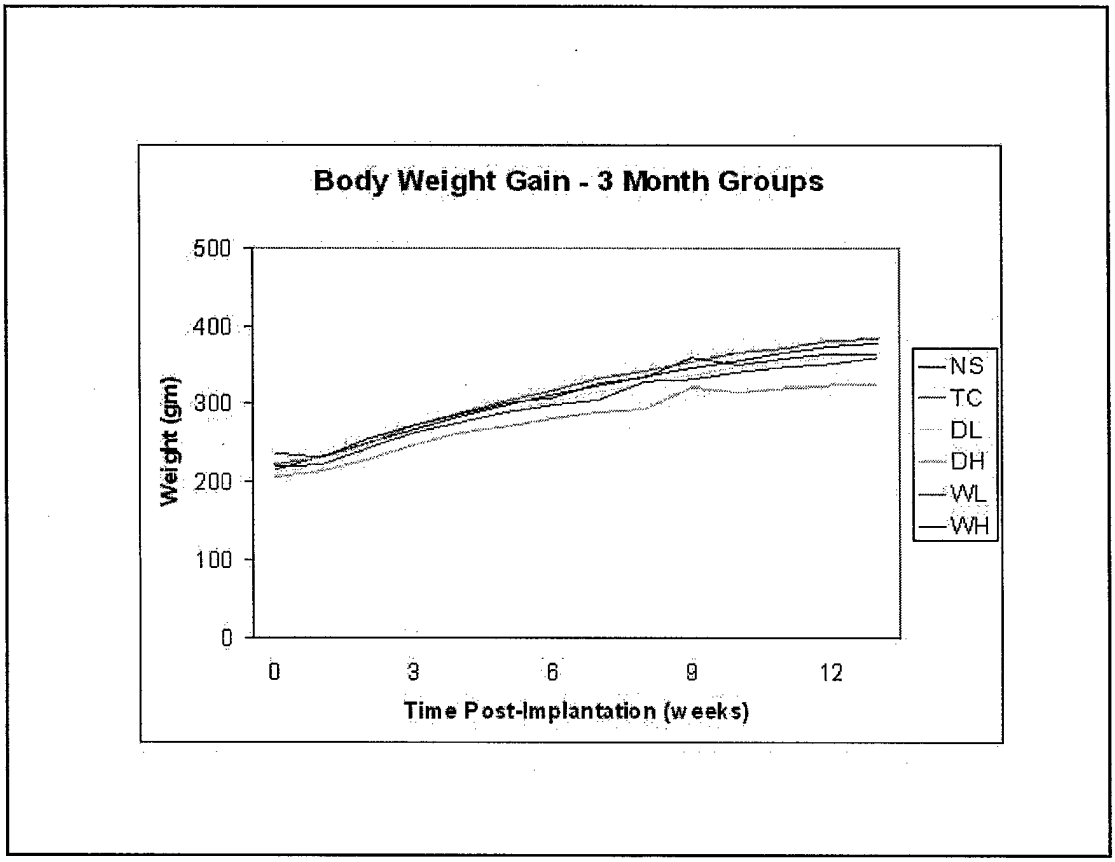
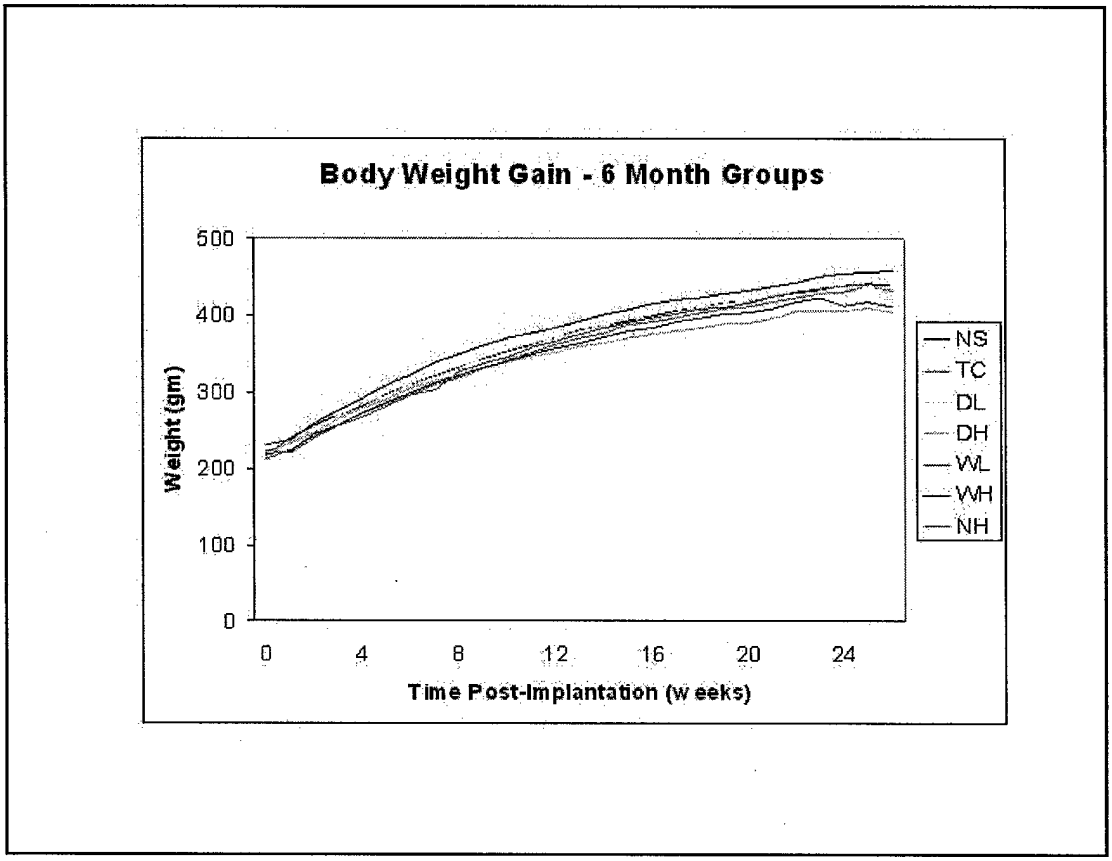

Body Weight Gain - 3 Month Groups
500
400
300
200
100
0
Weight (gm)
0
3
6
9
12
Time Post-Implantation (weeks)
NS
TC
DL
DH
WL
WH

Figure 3


Body Weight Gain - 6 Month Groups
Weight (gm)
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400
300
200
100
0
0
4
8
12
16
20
24
Time Post-Implantation (weeks)
NS
TC
DL
DH
WL
WH
NH

Figure 4

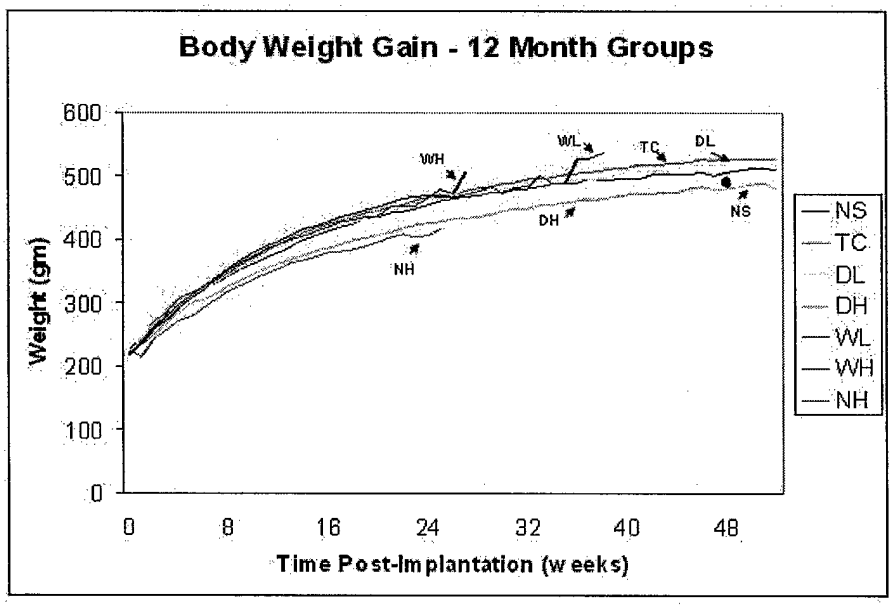
Body Weight Gain - 12 Month Groups
Weight (gm)
600
500
400
300
200
100
0
0
8
16
24
32
40
48
Time Post-Implantation (weeks)
WH
WL
TC
DL
NH
DH
NS
NS
TC
DL
DH
WL
WH
NH

Figure 5

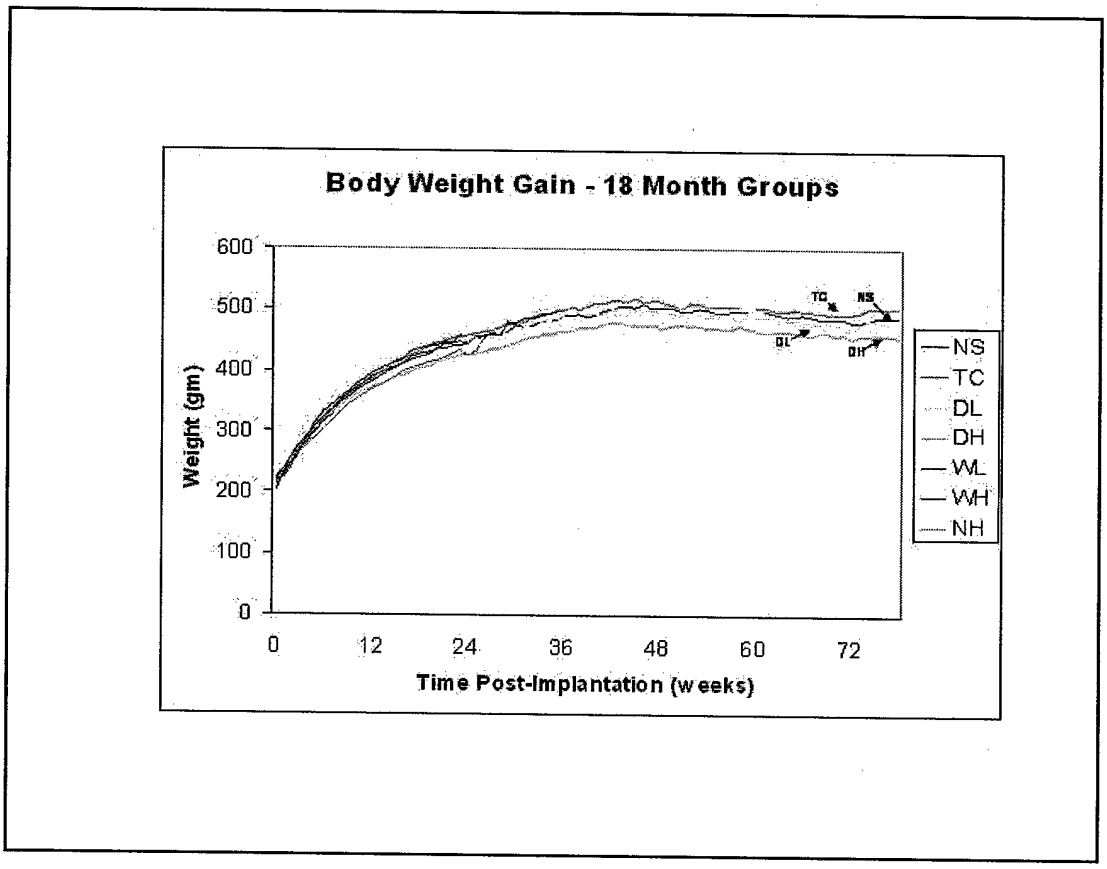
Body Weight Gain - 18 Month Groups
Weight (gm)
600
500
400
300
200
100
0
0
12
24
36
48
60
72
Time Post-Implantation (weeks)
NS
TC
DL
DH
WL
WH
NH

Figure 6

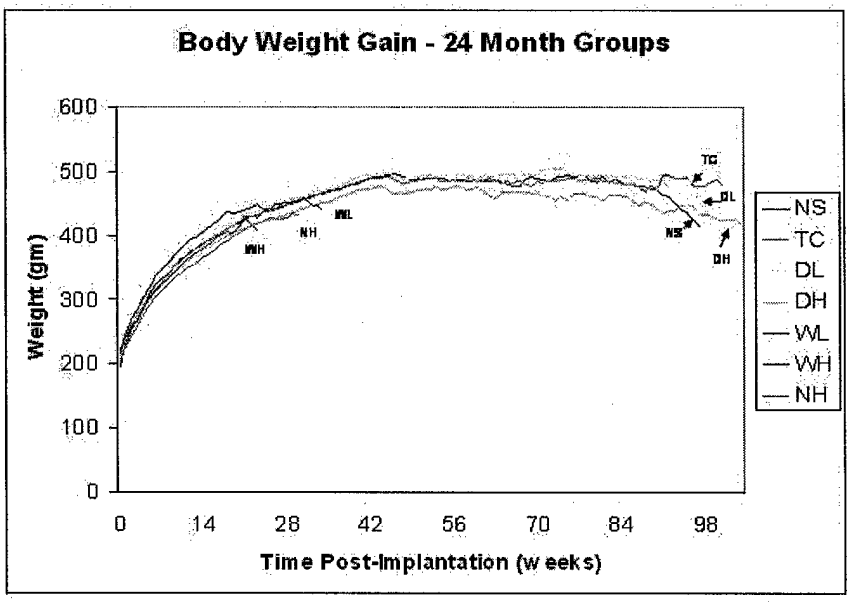
Body Weight Gain - 24 Month Groups
Weight (gm)
600
500
400
300
200
100
0
0
14
28
42
56
70
84
98
Time Post-Implantation (weeks)
NS
TC
DL
DH
WL
WH
NH

Table 2. Hematology Parameters for 1 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
WBC	3.6 ± 0.2	3.9 ± 0.2	4.5 ± 0.1	3.9 ± 0.1	3.8 ± 0.1	3.9 ± 0.2
RBC	7.5 ± 0.1	7.8 ± 0.1	7.9 ± 0.1	7.6 ± 0.1	7.7 ± 0.1	8.5 ± 0.1
HGB	13.7 ± 0.1	13.7 ± 0.2	14.1 ± 0.1	13.7 ± 0.2	14.8 ± 0.2	15.8 ± 0.1
HCT	37.9 ± 0.4	40.2 ± 0.4	40.2 ± 0.5	38.4 ± 0.5	39.7 ± 0.5	43.3 ± 0.4
MCV	50.8 ± 0.1	51.2 ± 0.1	50.7 ± 0.1	50.8 ± 0.2	51.2 ± 0.3	51.0 ± 0.2
MCH	18.4 ± 0.1	17.4 ± 0.1	17.9 ± 0.2	18.1 ± 0.1	19.1 ± 0.1	18.6 ± 0.2
MCHC	36.2 ± 0.2	34.0 ± 0.1	35.3 ± 0.4	35.6 ± 0.3	37.4 ± 0.3	36.6 ± 0.4
CHCM	32.7 ± 0.1	32.2 ± 0.1	33.0 ± 0.1	33.3 ± 0.3	33.4 ± 0.3	34.1 ± 0.1
CH	16.6 ± 0.1	16.5 ± 0.0	16.7 ± 0.1	16.9 ± 0.1	17.1 ± 0.1	17.3 ± 0.0
RDW	12.1 ± 0.3	12.2 ± 0.1	12.0 ± 0.1	12.5 ± 0.2	12.7 ± 0.1	14.2 ± 0.2
HDW	2.7 ± 0.1	2.3 ± 0.0	2.4 ± 0.1	2.5 ± 0.0	2.6 ± 0.0	2.8 ± 0.0
PLT	648.3 ± 52.6	646.5 ± 18.8	653.6 ± 11.9	735.4 ± 19.8	641.0 ± 18.0	756.2 ± 43.5
MPV	10.0 ± 1.6	7.9 ± 0.4	8.1 ± 0.3	8.6 ± 0.4	8.6 ± 0.4	9.9 ± 0.5

WBC (x10e6/ul):white blood cells; RBC (x10e6/ul):red blood cells; HGB (g/dL):hemoglobin; HCT (%):hematocrit; MCV (fL):mean corpuscular volume; MCH (pg):mean corpuscular hemoglobin; MCHC (g/dL):mean corpuscular hemoglobin concentration; CHCM (g/dL):cell hemoglobin concentration mean; CH (pg):cell hemoglobin; RDW (%): red cell distribution width; HDW (g/dL):hemoglobin distribution width; PLT (x10e3/ul):platelets; MPV (fL):mean platelet volume. Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 3. Cellular Hematology for 1 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
% Neut	20.1 ± 0.9	17.0 ± 0.9	16.9 ± 0.7	19.4 ± 0.9	21.0 ± 1.1	21.1 ± 0.9
%Lymph	74.8 ± 0.9	78.6 ± 1.1	78.9 ± 0.7	76.0 ± 1.0	74.7 ± 1.2	75.0 ± 0.9
%Mono	1.6 ± 0.1	1.5 ± 0.1	1.6 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	1.8 ± 0.1
%Eos	2.5 ± 0.2	1.8 ± 0.2	1.3 ± 0.1	2.2 ± 0.2	2.1 ± 0.2	1.2 ± 0.1
%Baso	0.7 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.2 ± 0.0
%Luc	0.3 ± 0.0	0.5 ± 0.1	0.8 ± 0.1	0.4 ± 0.0	0.5 ± 0.1	0.8 ± 0.1
#Neut	0.7 ± 0.0	0.7 ± 0.0	0.8 ± 0.0	0.7 ± 0.0	0.8 ± 0.0	0.8 ± 0.0
#Lymph	2.7 ± 0.1	3.0 ± 0.2	3.5 ± 0.1	3.0 ± 0.1	2.9 ± 0.1	2.9 ± 0.2
#Mono	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
#Eos	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.0 ± 0.0
#Baso	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
#Luc	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

%Neut:percent neutrophils; %Lymph:percent lymphocytes; %Mono:percent monocytes; %Eos:percent eosinophils; %Baso:percent basophils; %Luc:percent leucocytes; # Neut:neutrophils (x10e3/ul); # Lymph:lymphocytes (x10e3/ul); # Mono:monocytes (x10e3/ul); # Eos:eosinophils (x10e3/ul); # Baso:basophils (x10e3/ul); # Luc:leucocytes (x10e3/ul). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 4. Hematology Parameters for 3 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
WBC	3.4 ± 0.2	2.9 ± 0.2	1.4 ± 0.7	2.8 ± 0.3	4.1 ± 0.1	4.0 ± 0.2
RBC	7.5 ± 0.2	7.5 ± 0.1	7.0 ± 0.2	7.5 ± 0.2	8.5 ± 0.2	9.1 ± 0.7
HGB	12.5 ± 0.4	12.9 ± 0.1	12.3 ± 0.4	13.7 ± 0.3	15.5 ± 0.4	17.3 ± 0.1
HCT	37.4 ± 1.2	38.1 ± 0.3	35.1 ± 1.1	37.9 ± 0.8	42.1 ± 0.7	44.8 ± 3.5
MCV	49.8 ± 0.2	51.0 ± 0.4	50.0 ± 0.3	50.4 ± 0.2	49.7 ± 0.1	48.9 ± 0.4
MCH	16.7 ± 0.2	17.3 ± 0.1	17.5 ± 0.1	18.2 ± 0.1	18.3 ± 0.2	17.7 ± 0.1
MCHC	33.5 ± 0.3	33.8 ± 0.4	34.9 ± 0.1	36.0 ± 0.3	36.7 ± 0.3	35.9 ± 0.3
CHCM	32.7 ± 0.2	31.8 ± 0.2	32.3 ± 0.2	33.2 ± 0.2	33.9 ± 0.1	33.1 ± 0.7
CH	16.3 ± 0.0	16.2 ± 0.1	16.2 ± 0.0	16.7 ± 0.1	16.8 ± 0.1	16.1 ± 0.4
RDW	12.9 ± 0.2	12.8 ± 0.3	13.1 ± 0.1	12.6 ± 0.4	12.7 ± 0.1	13.6 ± 0.1
HDW	2.4 ± 0.1	2.4 ± 0.2	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.0	2.7 ± 0.0
PLT	470.8 ± 47.7	513.2 ± 38.4	496.4 ± 33.7	647.1 ± 40.6	585.1 ± 35.9	568.3 ± 7.5
MPV	8.8 ± 1.8	9.6 ± 1.1	10.9 ± 1.4	8.7 ± 0.4	9.1 ± 0.6	11.7 ± 0.5

WBC (x10e6/ul):white blood cells; RBC (x10e6/ul):red blood cells; HGB (g/dL):hemoglobin; HCT (%):hematocrit; MCV (fL):mean corpuscular volume; MCH (pg):mean corpuscular hemoglobin; MCHC (g/dL):mean corpuscular hemoglobin concentration; CHCM (g/dL):cell hemoglobin concentration mean; CH (pg):cell hemoglobin; RDW (%): red cell distribution width; HDW (g/dL):hemoglobin distribution width; PLT (x10e3/ul):platelets; MPV (fL):mean platelet volume. Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 5. Cellular Hematology for 3 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
% Neut	20.3 ± 2.0	21.9 ± 1.1	25.5 ± 2.3	22.5 ± 2.0	19.7 ± 0.9	23.2 ± 1.6
%Lymph	69.5 ± 2.3	72.8 ± 1.2	59.2 ± 2.7	70.6 ± 3.0	75.3 ± 1.1	71.2 ± 1.7
%Mono	2.7 ± 1.2	1.5 ± 0.2	2.1 ± 0.3	1.9 ± 0.2	1.7 ± 0.1	2.0 ± 0.2
%Eos	7.9 ± 1.8	3.2 ± 0.3	11.0 ± 1.4	3.4 ± 1.0	2.2 ± 0.2	2.3 ± 0.2
%Baso	0.6 ± 0.1	0.5 ± 0.2	2.0 ± 0.5	0.7 ± 0.1	0.4 ± 0.1	0.6 ± 0.1
%Luc	0.2 ± 0.0	0.1 ± 0.0	0.3 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.7 ± 0.1
#Neut	0.7 ± 0.1	0.6 ± 0.0	0.3 ± 0.1	0.6 ± 0.0	0.8 ± 0.0	0.9 ± 0.1
#Lymph	2.4 ± 0.2	2.1 ± 0.2	0.9 ± 0.4	2.1 ± 0.2	3.1 ± 0.1	2.8 ± 0.2
#Mono	0.1 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
#Eos	0.3 ± 0.1	0.1 ± 0.0	0.2 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
#Baso	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
#Luc	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

%Neut:percent neutrophils; %Lymph:percent lymphocytes; %Mono:percent monocytes; %Eos:percent eosinophils; %Baso:percent basophils; %Luc:percent leucocytes; # Neut:neutrophils (x10e3/ul); # Lymph:lymphocytes (x10e3/ul); # Mono:monocytes (x10e3/ul); # Eos:eosinophils (x10e3/ul); # Baso:basophils (x10e3/ul); # Luc:leucocytes (x10e3/ul). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 6. Hematology Parameters for 6 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High	Nickel
WBC	3.4 ± 0.2	3.2 ± 0.2	3.3 ± 0.2	2.5 ± 0.2	3.9 ± 0.4	4.6 ± 0.3	2.6 ± 0.2
RBC	8.3 ± 0.1	8.3 ± 0.1	8.2 ± 0.1	7.8 ± 0.2	8.0 ± 0.2	10.1 ± 0.1	7.5 ± 0.1
HGB	14.3 ± 0.1	14.5 ± 0.1	14.3 ± 0.1	14.1 ± 0.4	13.9 ± 0.4	16.5 ± 0.3	12.9 ± 0.2
HCT	41.8 ± 0.5	41.8 ± 0.5	40.7 ± 0.3	38.6 ± 1.1	40.4 ± 1.0	50.2 ± 0.4	38.1 ± 0.8
MCV	50.2 ± 0.1	50.2 ± 0.2	49.9 ± 0.2	49.6 ± 0.1	50.3 ± 0.3	49.7 ± 0.2	51.1 ± 0.7
MCH	17.3 ± 0.1	17.5 ± 0.1	17.6 ± 0.1	18.0 ± 0.1	17.3 ± 0.1	16.3 ± 0.3	17.4 ± 0.1
MCHC	34.4 ± 0.2	34.8 ± 0.4	35.2 ± 0.3	36.4 ± 0.1	34.5 ± 0.3	32.8 ± 0.6	34.1 ± 0.5
CHCM	32.0 ± 0.1	32.0 ± 0.1	32.5 ± 0.1	33.0 ± 0.0	32.2 ± 0.2	32.2 ± 0.1	31.7 ± 0.5
CH	16.1 ± 0.0	16.1 ± 0.0	16.2 ± 0.0	16.4 ± 0.0	16.1 ± 0.0	16.0 ± 0.0	16.1 ± 0.1
RDW	12.9 ± 0.1	12.5 ± 0.1	12.5 ± 0.1	12.9 ± 0.4	13.1 ± 0.1	13.8 ± 0.1	13.0 ± 0.2
HDW	2.3 ± 0.0	2.2 ± 0.0	2.3 ± 0.0	2.4 ± 0.1	2.4 ± 0.0	2.5 ± 0.0	2.4 ± 0.1
PLT	559 ± 14	562 ± 15	530 ± 31	573 ± 42	542 ± 14	468 ± 18	487 ± 26
MPV	8.7 ± 0.4	9.9 ± 0.7	8.2 ± 0.5	8.1 ± 0.5	8.7 ± 0.5	10.1 ± 0.6	9.0 ± 0.5

WBC (x10e6/ul):white blood cells; RBC (x10e6/ul):red blood cells; HGB (g/dL):hemoglobin; HCT (%):hematocrit; MCV (fL):mean corpuscular volume; MCH (pg):mean corpuscular hemoglobin; MCHC (g/dL):mean corpuscular hemoglobin concentration; CHCM (g/dL):cell hemoglobin concentration mean; CH (pg):cell hemoglobin; RDW (%): red cell distribution width; HDW (g/dL):hemoglobin distribution width; PLT (x10e3/ul):platelets; MPV (fL):mean platelet volume. Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 7. Cellular Hematology for 6 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High	Nickel
% Neut	29.3 ± 2.3	25.4 ± 0.8	27.5 ± 1.0	29.2 ± 1.9	30.5 ± 2.4	29.3 ± 1.6	29.5 ± 2.1
%Lymph	64.5 ± 2.5	68.6 ± 0.9	65.7 ± 1.3	65.0 ± 1.9	63.8 ± 2.4	63.9 ± 1.9	64.7 ± 2.4
%Mono	2.1 ± 0.2	2.1 ± 0.1	2.3 ± 0.2	1.7 ± 0.1	2.1 ± 0.1	2.7 ± 0.2	2.0 ± 0.3
%Eos	2.9 ± 0.2	2.7 ± 0.2	2.9 ± 0.2	2.7 ± 0.2	2.3 ± 0.1	2.7 ± 0.2	2.7 ± 0.3
%Baso	0.6 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.6 ± 0.0	0.7 ± 0.1
%Luc	0.6 ± 0.1	0.6 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.6 ± 0.1	0.8 ± 0.1	0.6 ± 0.1
#Neut	1.0 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.7 ± 0.1	1.3 ± 0.3	1.3 ± 0.1	0.8 ± 0.1
#Lymph	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.1	1.6 ± 0.1	2.4 ± 0.2	2.9 ± 0.2	1.6 ± 0.1
#Mono	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
#Eos	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
#Baso	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
#Luc	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

%Neut:percent neutrophils; %Lymph:percent lymphocytes; %Mono:percent monocytes; %Eos:percent eosinophils; %Baso:percent basophils; %Luc:percent leucocytes; # Neut:neutrophils (x10e3/ul); # Lymph:lymphocytes (x10e3/ul); # Mono:monocytes (x10e3/ul); # Eos:eosinophils (x10e3/ul); # Baso:basophils (x10e3/ul); # Luc:leucocytes (x10e3/ul). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 8. Hematology Parameters for 12 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High
WBC	2.8 ± 0.1	2.6 ± 0.1	2.6 ± 0.2	2.3 ± 0.3
RBC	7.6 ± 0.1	7.6 ± 0.0	7.6 ± 0.1	7.3 ± 0.1
HGB	13.1 ± 0.1	13.2 ± 0.1	12.6 ± 0.2	12.5 ± 0.2
HCT	38.6 ± 0.5	38.4 ± 0.2	37.9 ± 0.5	36.1 ± 0.5
MCV	50.7 ± 0.2	50.3 ± 0.1	49.8 ± 0.2	49.4 ± 0.2
MCH	17.2 ± 0.1	17.3 ± 0.0	16.5 ± 0.3	17.1 ± 0.1
MCHC	34.0 ± 0.2	34.3 ± 0.1	33.2 ± 0.6	34.6 ± 0.1
CHCM	31.5 ± 0.1	31.5 ± 0.1	31.8 ± 0.1	32.2 ± 0.1
CH	15.9 ± 0.1	15.8 ± 0.1	15.8 ± 0.1	15.9 ± 0.1
RDW	13.2 ± 0.1	13.3 ± 0.1	12.9 ± 0.1	12.7 ± 0.1
HDW	2.3 ± 0.1	2.4 ± 0.1	2.3 ± 0.1	2.3 ± 0.0
PLT	621 ± 15	584 ± 18	533 ± 26	530 ± 13
MPV	9.7 ± 0.7	9.4 ± 0.6	9.0 ± 0.5	8.8 ± 0.5

WBC (x10e6/ul):white blood cells; RBC (x10e6/ul):red blood cells; HGB (g/dL):hemoglobin; HCT (%):hematocrit; MCV (fL):mean corpuscular volume; MCH (pg):mean corpuscular hemoglobin; MCHC (g/dL):mean corpuscular hemoglobin concentration; CHCM (g/dL):cell hemoglobin concentration mean; CH (pg):cell hemoglobin; RDW (%): red cell distribution width; HDW (g/dL):hemoglobin distribution width; PLT (x10e3/ul):platelets; MPV (fL):mean platelet volume. Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 9. Cellular Hematology for 12 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High
% Neut	34.1 ± 1.6	34.8 ± 1.2	33.5 ± 1.6	38.9 ± 2.1
%Lymph	59.3 ± 1.8	57.7 ± 1.5	58.8 ± 2.0	50.6 ± 2.9
%Mono	2.5 ± 0.1	2.8 ± 0.2	2.9 ± 0.2	2.7 ± 0.2
%Eos	3.0 ± 0.3	3.7 ± 0.6	4.0 ± 0.7	6.1 ± 1.0
%Baso	0.7 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	1.4 ± 0.2
%Luc	0.3 ± 0.0	0.4 ± 0.1	0.3 ± 0.0	0.6 ± 0.1
#Neut	0.9 ± 0.1	0.9 ± 0.0	0.9 ± 0.1	0.9 ± 0.2
#Lymph	1.6 ± 0.1	1.5 ± 0.1	1.6 ± 0.1	1.2 ± 0.2
#Mono	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
#Eos	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
#Baso	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
#Luc	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

%Neut:percent neutrophils; %Lymph:percent lymphocytes; %Mono:percent monocytes; %Eos:percent eosinophils; %Baso:percent basophils; %Luc:percent leucocytes; # Neut:neutrophils (x10e3/ul); # Lymph:lymphocytes (x10e3/ul); # Mono:monocytes (x10e3/ul); # Eos:eosinophils (x10e3/ul); # Baso:basophils (x10e3/ul); # Luc:leucocytes (x10e3/ul). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 10. Hematology Parameters for 18 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High
WBC	2.8 ± 1.4	1.1 ± 0.4	10.6 ± 7.3	0.7 ± 0.1
RBC	7.2 ± 0.3	7.3 ± 0.3	6.5 ± 0.8	7.4 ± 0.1
HGB	13.5 ± 0.4	13.2 ± 0.7	11.8 ± 1.2	12.7 ± 0.2
HCT	37.7 ± 1.1	36.6 ± 1.7	34.8 ± 2.4	35.6 ± 0.4
MCV	50.4 ± 0.8	49.7 ± 0.4	120.5 ± 61.2	48.4 ± 0.6
MCH	18.0 ± 0.3	17.9 ± 0.2	18.7 ± 0.9	17.3 ± 0.2
MCHC	35.8 ± 0.2	36.0 ± 0.2	33.2 ± 1.5	35.8 ± 0.2
CHCM	33.5 ± 0.5	34.1 ± 0.3	33.2 ± 0.7	34.3 ± 0.3
CH	16.8 ± 0.1	16.9 ± 0.1	18.9 ± 1.5	16.5 ± 0.1
RDW	14.2 ± 0.2	13.7 ± 0.3	15.6 ± 1.1	13.3 ± 0.1
HDW	2.7 ± 0.1	2.7 ± 0.1	3.2 ± 0.3	2.7 ± 0.1
PLT	616 ± 63	605 ± 17	505 ± 53	538 ± 22
MPV	10.9 ± 2.0	7.6 ± 0.3	8.0 ± 0.5	8.4 ± 0.6

WBC (x10e6/ul):white blood cells; RBC (x10e6/ul):red blood cells; HGB (g/dL):hemoglobin; HCT (%):hematocrit; MCV (fL):mean corpuscular volume; MCH (pg):mean corpuscular hemoglobin; MCHC (g/dL):mean corpuscular hemoglobin concentration; CHCM (g/dL):cell hemoglobin concentration mean; CH (pg):cell hemoglobin; RDW (%): red cell distribution width; HDW (g/dL):hemoglobin distribution width; PLT (x10e3/ul):platelets; MPV (fL):mean platelet volume. Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table11. Cellular Hematology for 18 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High
% Neut	41.0 ± 3.6	42.6 ± 2.5	39.6 ± 8.5	48.1 ± 2.5
%Lymph	47.0 ± 3.8	45.6 ± 2.8	37.4 ± 8.6	39.9 ± 2.8
%Mono	4.0 ± 0.6	4.1 ± 0.3	4.0 ± 0.4	3.3 ± 0.2
%Eos	6.2 ± 1.5	6.4 ± 1.1	7.5 ± 2.6	6.3 ± 0.6
%Baso	1.2 ± 0.3	0.5 ± 0.1	1.5 ± 0.7	0.6 ± 0.1
%Luc	1.0 ± 0.3	0.9 ± 0.2	10.8 ± 9.5	0.4 ± 0.1
#Neut	0.8 ± 0.3	0.5 ± 0.2	1.1 ± 0.5	0.3 ± 0.0
#Lymph	1.6 ± 1.0	0.5 ± 0.2	3.8 ± 2.4	0.3 ± 0.0
#Mono	0.1 ± 0.1	0.1 ± 0.0	0.4 ± 0.3	0.0 ± 0.0
#Eos	0.1 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	0.0 ± 0.0
#Baso	0.0 ± 0.0	0.0 ± 0.0	0.5 ± 0.4	0.0 ± 0.0
#Luc	0.0 ± 0.0	0.0 ± 0.0	5.1 ± 5.0	0.0 ± 0.0

%Neut:percent neutrophils; %Lymph:percent lymphocytes; %Mono:percent monocytes; %Eos:percent eosinophils; %Baso:percent basophils; %Luc:percent leucocytes; # Neut:neutrophils (x10e3/ul); # Lymph:lymphocytes (x10e3/ul); # Mono:monocytes (x10e3/ul); # Eos:eosinophils (x10e3/ul); # Baso:basophils (x10e3/ul); # Luc:leucocytes (x10e3/ul). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 12. Hematology Parameters for 24 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High
WBC	20.2 ± 10.2	3.0 ± 0.7	28.1 ± 25.0	11.1 ± 6.0
RBC	5.1 ± 1.0	6.9 ± 0.4	7.1 ± 0.9	6.8 ± 0.4
HGB	9.8 ± 1.4	13.6 ± 0.6	13.4 ± 1.7	12.3 ± 0.7
HCT	31.6 ± 2.9	37.0 ± 1.6	37.8 ± 4.8	35.9 ± 1.7
MCV	75.3 ± 13.8	53.9 ± 1.2	52.9 ± 1.0	52.9 ± 0.7
MCH	21.3 ± 2.1	19.9 ± 1.0	18.8 ± 0.5	18.0 ± 0.4
MCHC	30.2 ± 2.0	36.9 ± 1.3	35.5 ± 0.4	34.1 ± 0.6
CHCM	29.6 ± 1.3	31.3 ± 0.4	32.2 ± 0.9	32.1 ± 0.3
CH	21.2 ± 2.7	16.7 ± 0.2	17.1 ± 0.3	16.9 ± 0.3
RDW	17.5 ± 1.1	14.8 ± 0.4	14.7 ± 1.9	15.1 ± 1.0
HDW	3.1 ± 0.3	2.7 ± 0.1	2.3 ± 0.0	2.7 ± 0.2
PLT	523 ± 113	1063 ± 280	650 ± 129	611 ± 29
MPV	10.7 ± 1.7	13.5 ± 3.9	12.6 ± 3.3	8.1 ± 0.5

WBC (x10e6/ul):white blood cells; RBC (x10e6/ul):red blood cells; HGB (g/dL):hemoglobin; HCT (%):hematocrit; MCV (fL):mean corpuscular volume; MCH (pg):mean corpuscular hemoglobin; MCHC (g/dL):mean corpuscular hemoglobin concentration; CHCM (g/dL):cell hemoglobin concentration mean; CH (pg):cell hemoglobin; RDW (%): red cell distribution width; HDW (g/dL):hemoglobin distribution width; PLT (x10e3/ul):platelets; MPV (fL):mean platelet volume. Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 13. Cellular Hematology for 24 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High
% Neut	26.7 ± 6.2	47.0 ± 4.6	42.3 ± 5.2	54.5 ± 5.1
%Lymph	61.2 ± 6.3	43.8 ± 5.8	40.8 ± 6.9	35.4 ± 5.3
%Mono	4.2 ± 0.9	2.6 ± 0.3	9.6 ± 5.3	3.7 ± 0.6
%Eos	3.7 ± 2.3	5.2 ± 1.7	1.5 ± 0.3	4.7 ± 1.4
%Baso	1.4 ± 0.5	2.1 ± 0.6	5.1 ± 4.3	0.9 ± 0.4
%Luc	2.8 ± 1.3	0.3 ± 0.1	1.0 ± 0.3	0.9 ± 0.3
#Neut	3.1 ± 1.1	1.3 ± 0.3	7.3 ± 5.9	7.1 ± 4.0
#Lymph	14.6 ± 7.9	1.5 ± 0.5	4.5 ± 3.1	3.4 ± 1.9
#Mono	1.1 ± 0.7	0.1 ± 0.0	9.3 ± 9.2	0.4 ± 0.2
#Eos	0.2 ± 0.1	0.1 ± 0.0	0.2 ± 0.1	0.1 ± 0.0
#Baso	0.3 ± 0.2	0.1 ± 0.0	6.8 ± 6.7	0.0 ± 0.0
#Luc	0.9 ± 0.7	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

%Neut:percent neutrophils; %Lymph:percent lymphocytes; %Mono:percent monocytes; %Eos:percent eosinophils; %Baso:percent basophils; %Luc:percent leucocytes; # Neut:neutrophils (x10e3/ul); # Lymph:lymphocytes (x10e3/ul); # Mono:monocytes (x10e3/ul); # Eos:eosinophils (x10e3/ul); # Baso:basophils (x10e3/ul); # Luc:leucocytes (x10e3/ul). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 14. Serum Chemistries for 1 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
GLU	206.8 ± 18.3	217.3 ± 8.7	232.1 ± 10.0	191.6 ± 9.7	171.1 ± 9.2	206.8 ± 7.1
BUN	13.2 ± 1.1	14.5 ± 0.5	13.9 ± 0.4	14.9 ± 0.4	13.1 ± 0.4	16.9 ± 0.3
CREA	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.5 ± 0.0
NA	170.1 ± 13.0	160.3 ± 8.1	159.9 ± 8.2	163.4 ± 9.9	140.2 ± 0.7	145.9 ± 0.7
K	4.1 ± 0.3	4.0 ± 0.1	3.9 ± 0.1	4.1 ± 0.1	3.6 ± 0.1	4.4 ± 0.1
CA	9.5 ± 0.5	9.4 ± 0.1	9.6 ± 0.1	9.2 ± 0.2	7.9 ± 0.4	10.4 ± 0.1
PHOS	5.9 ± 0.3	6.3 ± 0.2	6.7 ± 0.1	6.5 ± 0.3	5.3 ± 0.3	6.9 ± 0.2
URIC	1.4 ± 0.4	0.5 ± 0.0	0.5 ± 0.1	0.8 ± 0.1	0.6 ± 0.1	0.9 ± 0.1
Tot Pro	4.9 ± 0.3	5.1 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	4.9 ± 0.1	5.8 ± 0.1
ALB	2.2 ± 0.2	2.3 ± 0.1	2.3 ± 0.0	2.2 ± 0.1	2.0 ± 0.1	2.7 ± 0.0
LDH	2679 ± 950	3274 ± 565	3501 ± 511	3328 ± 656	2312 ± 370	2146 ± 389
ALKP	276.4 ± 25.1	289.2 ± 11.8	287.3 ± 12.4	239.1 ± 17.9	176.8 ± 10.0	260.0 ± 5.9

GLU:glucose (mg/dL); BUN:blood urea nitrogen (mg/dL); CREA:creatinine (mg/dL); NA:sodium (mmol/L); K:potassium (mmol/L); CA:calcium (mg/dL); PHOS:phosphorus (mg/dL); URIC:uric acid (mg/dL); Tot Pro:total protein (g/dL); ALB:albumin (g/dL); LDH;lactate dehydrogenase (U/L); ALKP:alkaline phosphatase (U/L). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 15. Serum Chemistries for 3 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
GLU	241.6 ± 20.9	214.4 ± 6.8	242.9 ± 7.5	186.9 ± 7.2	215.7 ± 8.5	217.4 ± 9.9
BUN	18.4 ± 1.5	17.6 ± 0.5	18.2 ± 0.5	15.7 ± 0.3	16.3 ± 0.5	16.0 ± 0.6
CREA	0.6 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0
NA	180.9 ± 8.6	136.6 ± 0.5	142.3 ± 3.6	181.8 ± 1.9	181.9 ± 1.7	172.0 ± 5.0
K	4.2 ± 0.2	4.0 ± 0.1	4.3 ± 0.1	3.6 ± 0.1	3.7 ± 0.1	3.9 ± 0.1
CA	9.6 ± 0.7	9.6 ± 0.2	10.2 ± 0.2	9.0 ± 0.2	8.9 ± 0.2	9.7 ± 0.4
PHOS	5.2 ± 0.4	5.3 ± 0.2	6.1 ± 0.2	4.3 ± 0.1	4.7 ± 0.3	5.1 ± 0.3
URIC	1.0 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.6 ± 0.1	0.8 ± 0.1
Tot Pro	5.4 ± 0.3	5.6 ± 0.1	5.8 ± 0.1	5.0 ± 0.1	5.5 ± 0.1	5.6 ± 0.2
ALB	2.6 ± 0.2	2.7 ± 0.1	2.9 ± 0.1	2.1 ± 0.1	2.1 ± 0.1	2.5 ± 0.2
LDH	2719 ± 462	2933 ± 372	2536 ± 358	2110 ± 343	2318 ± 285	2519 ± 273
ALKP	180.9 ± 17.0	200.0 ± 7.2	200.8 ± 8.6	148.9 ± 4.9	163.7 ± 7.9	163.0 ± 11.7

GLU:glucose (mg/dL); BUN:blood urea nitrogen (mg/dL); CREA:creatinine (mg/dL); NA:sodium (mmol/L); K:potassium (mmol/L); CA:calcium (mg/dL); PHOS:phosphorus (mg/dL); URIC:uric acid (mg/dL); Tot Pro:total protein (g/dL); ALB:albumin (g/dL); LDH;lactate dehydrogenase (U/L); ALKP:alkaline phosphatase (U/L). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 16. Serum Chemistries for 6 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High	Nickel
GLU	229.4 ± 7.1	245.8 ± 9.2	246.7 ± 6.6	241.6 ± 3.3	246.6 ± 4.1	230.5 ± 4.3	248.1 ± 8.3
BUN	16.5 ± 0.3	16.5 ± 0.3	16.1 ± 0.5	15.9 ± 0.7	14.5 ± 0.6	13.5 ± 0.5	12.9 ± 0.3
CREA	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.4 ± 0.0
NA	138.0 ± 0.3	139.1 ± 0.7	137.8 ± 0.3	138.6 ± 0.3	137.9 ± 0.4	138.3 ± 0.3	138.9 ± 0.6
K	4.7 ± 0.2	4.7 ± 0.2	4.7 ± 0.1	4.3 ± 0.1	4.2 ± 0.1	4.1 ± 0.1	4.0 ± 0.1
CA	10.1 ± 0.0	10.0 ± 0.1	9.9 ± 0.0	10.0 ± 0.1	10.0 ± 0.1	9.9 ± 0.0	10.1 ± 0.1
PHOS	5.4 ± 0.2	4.9 ± 0.2	5.3 ± 0.2	5.4 ± 0.2	5.1 ± 0.1	5.0 ± 0.2	5.2 ± 0.2
URIC	1.2 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.5 ± 0.1	0.7 ± 0.1
Tot Pro	6.2 ± 0.1	6.2 ± 0.1	6.1 ± 0.1	5.8 ± 0.1	5.7 ± 0.0	5.7 ± 0.1	5.6 ± 0.0
ALB	2.9 ± 0.0	2.9 ± 0.1	2.8 ± 0.1	2.6 ± 0.1	2.6 ± 0.0	2.5 ± 0.0	2.5 ± 0.0
LDH	6876 ± 585	6654 ± 543	6706 ± 629	5253 ± 806	4727 ± 452	4241 ± 454	3165 ± 498
ALKP	216.2 ± 5.8	223.6 ± 4.9	199.7 ± 7.9	207.0 ± 10.3	212.6 ± 8.9	190.3 ± 5.3	229.5 ± 10.7

GLU:glucose (mg/dL); BUN:blood urea nitrogen (mg/dL); CREA:creatinine (mg/dL); NA:sodium (mmol/L); K:potassium (mmol/L); CA:calcium (mg/dL); PHOS:phosphorus (mg/dL); URIC:uric acid (mg/dL); Tot Pro:total protein (g/dL); ALB:albumin (g/dL); LDH;lactate dehydrogenase (U/L); ALKP:alkaline phosphatase (U/L). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 17. Serum Chemistries for 12 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High
GLU	247.1 ± 6.1	232.1 ± 5.2	213.2 ± 6.2	220.6 ± 10.7
BUN	15.4 ± 0.6	16.0 ± 0.7	15.7 ± 0.8	17.1 ± 1.1
CREA	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.6 ± 0.0
NA	142.7 ± 0.9	146.0 ± 2.4	146.7 ± 4.3	169.6 ± 7.1
K	4.2 ± 0.0	4.3 ± 0.1	4.5 ± 0.1	4.2 ± 0.1
CA	10.2 ± 0.1	10.4 ± 0.2	10.0 ± 0.2	9.9 ± 0.4
PHOS	4.9 ± 0.1	4.6 ± 0.2	4.7 ± 0.1	4.5 ± 0.3
URIC	0.8 ± 0.1	0.7 ± 0.0	0.8 ± 0.1	0.7 ± 0.1
Tot Pro	5.8 ± 0.1	6.0 ± 0.1	5.8 ± 0.2	6.0 ± 0.2
ALB	2.8 ± 0.0	3.0 ± 0.1	2.8 ± 0.1	2.7 ± 0.2
LDH	4321 ± 512	5044 ± 548	4456 ± 622	3818 ± 536
ALKP	178.8 ± 7.6	194.6 ± 7.4	174.4 ± 9.0	171.0 ± 10.7

GLU:glucose (mg/dL); BUN:blood urea nitrogen (mg/dL); CREA:creatinine (mg/dL); NA:sodium (mmol/L); K:potassium (mmol/L); CA:calcium (mg/dL); PHOS:phosphorus (mg/dL); URIC:uric acid (mg/dL); Tot Pro:total protein (g/dL); ALB:albumin (g/dL); LDH;lactate dehydrogenase (U/L); ALKP:alkaline phosphatase (U/L). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 18. Serum Chemistries for 18 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High
GLU	162.1 ± 12.4	157.4 ± 14.8	155.8 ± 13.7	177.6 ± 12.5
BUN	15.9 ± 0.9	15.1 ± 1.5	13.6 ± 0.7	15.8 ± 0.9
CREA	0.6 ± 0.0	0.6 ± 0.1	0.5 ± 0.0	0.6 ± 0.0
NA	157.1 ± 10.3	165.8 ± 11.1	168.9 ± 10.7	157.3 ± 9.0
K	4.9 ± 0.2	5.0 ± 0.3	4.4 ± 0.2	4.5 ± 0.2
CA	10.5 ± 0.5	10.1 ± 0.8	9.7 ± 0.2	10.6 ± 0.2
PHOS	4.7 ± 0.3	4.3 ± 0.5	4.2 ± 0.3	4.5 ± 0.3
URIC	0.8 ± 0.1	0.6 ± 0.1	0.9 ± 0.2	0.6 ± 0.1
Tot Pro	6.7 ± 0.3	6.3 ± 0.6	5.8 ± 0.2	6.6 ± 0.3
ALB	3.0 ± 0.1	2.9 ± 0.3	2.5 ± 0.1	3.1 ± 0.1
LDH	4737 ± 406	3258 ± 693	4162 ± 585	3277 ± 595
ALKP	211.0 ± 20.9	174.7 ± 24.0	191.1 ± 20.1	190.3 ± 5.8

GLU:glucose (mg/dL); BUN:blood urea nitrogen (mg/dL); CREA:creatinine (mg/dL); NA:sodium (mmol/L); K:potassium (mmol/L); CA:calcium (mg/dL); PHOS:phosphorus (mg/dL); URIC:uric acid (mg/dL); Tot Pro:total protein (g/dL); ALB:albumin (g/dL); LDH;lactate dehydrogenase (U/L); ALKP:alkaline phosphatase (U/L). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 19. Serum Chemistries for 24 Month Rodents

	Non-Surgical	Tantalum	DU-Low	DU-High
GLU	148.5 ± 15.8	179.7 ± 16.1	181.7 ± 20.5	192.9 ± 12.0
BUN	16.8 ± 1.5	19.1 ± 0.9	18.5 ± 1.2	18.6 ± 1.2
CREA	0.6 ± 0.0	0.7 ± 0.1	0.6 ± 0.0	0.7 ± 0.1
NA	139.8 ± 2.5	146.6 ± 2.0	156.3 ± 3.3	146.7 ± 5.1
K	4.3 ± 0.2	4.6 ± 0.1	4.6 ± 0.2	4.1 ± 0.1
CA	10.0 ± 0.3	10.6 ± 0.1	11.1 ± 0.2	10.6 ± 0.3
PHOS	5.1 ± 0.3	4.8 ± 0.2	5.5 ± 0.2	5.0 ± 0.3
URIC	1.0 ± 0.1	1.1 ± 0.1	0.7 ± 0.1	0.8 ± 0.2
Tot Pro	5.5 ± 0.1	6.1 ± 0.1	6.4 ± 0.2	5.9 ± 0.2
ALB	2.6 ± 0.1	2.9 ± 0.1	3.3 ± 0.1	2.9 ± 0.2
LDH	3566 ± 659	3328 ± 626	3325 ± 639	1987 ± 579
ALKP	172.8 ± 22.4	181.1 ± 19.0	177.2 ± 22.2	204.3 ± 23.1

GLU:glucose (mg/dL); BUN:blood urea nitrogen (mg/dL); CREA:creatinine (mg/dL); NA:sodium (mmol/L); K:potassium (mmol/L); CA:calcium (mg/dL); PHOS:phosphorus (mg/dL); URIC:uric acid (mg/dL); Tot Pro:total protein (g/dL); ALB:albumin (g/dL); LDH;lactate dehydrogenase (U/L); ALKP:alkaline phosphatase (U/L). Data represent the mean of 15 observations. Errors are given as standard error of the mean.

Table 20. Organ Weights and Organ/Body Weight Ratios for 1-Month Rodents

1 Month	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
Spleen (mg)	652 ± 10	682 ± 13	710 ± 9 *	666 ± 20	725 ± 15 *	790 ± 14 *
Thymus (mg)	316 ± 11	308 ± 11	359 ± 16	309 ± 15	342 ± 13	307 ± 10
Liver (gm)	9.1 ± 0.2	10.0 ± 0.2	10.6 ± 0.2 *	9.7 ± 0.3	10.3 ± 0.1 *	9.9 ± 0.3 *
Kidney (mg)	806 ± 17	892 ± 18	957 ± 17	846 ± 19	909 ± 12 *	856 ± 15 *
Testes (mg)	1393 ± 21	1457 ± 19	1520 ± 15 *	1437 ± 23	1478 ± 15 *	1442 ± 19
Spleen/BW	2.4 ± 0.0	2.4 ± 0.1	2.3 ± 0.0	2.4 ± 0.0	2.4 ± 0.0	2.7 ± 0.0 *
Thymus/BW	1.2 ± 0.0	1.1 ± 0.0	1.2 ± 0.0	1.1 ± 0.0	1.1 ± 0.0	1.1 ± 0.0
Liver/BW	33.6 ± 0.2	34.5 ± 0.3	34.2 ± 0.2	34.2 ± 0.4	34.3 ± 0.2 *	34.2 ± 0.6
Kidney/BW	5.9 ± 0.1	6.2 ± 0.1	6.2 ± 0.1 *	6.0 ± 0.1	6.1 ± 0.1	5.9 ± 0.1
Testes/BW	10.3 ± 0.1	10.1 ± 0.2	9.9 ± 0.1 *	10.2 ± 0.1	9.9 ± 0.1 *	10.0 ± 0.1

Data are expressed as mean +/- standard error of the mean of 15 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test.

Table 21. Organ Weights and Organ/Body Weight Ratios for 3-Month Rodents

3 Month	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
Spleen (mg)	775 ± 10	795 ± 21	774 ± 14	719 ± 24 *	774 ± 13	909 ± 21 *
Thymus (mg)	278 ± 11	281 ± 13	249 ± 8	215 ± 16 *	303 ± 9	252 ± 13
Liver (gm)	11.5 ± 0.2	11.7 ± 0.2	11.2 ± 0.2	9.6 ± 0.2 *	11.2 ± 0.3	11.2 ± 0.3
Kidney (mg)	998 ± 17	1041 ± 14	1025 ± 23	883 ± 24 *	1029 ± 37	1047 ± 26
Testes (mg)	1536 ± 25	1599 ± 19	1539 ± 26	1474 ± 29	1484 ± 97	1525 ± 36
Spleen/BW	2.1 ± 0.0	2.1 ± 0.0	2.1 ± 0.0	2.2 ± 0.1	2.2 ± 0.0 *	2.5 ± 0.0 *
Thymus/BW	0.7 ± 0.0	0.7 ± 0.0	0.7 ± 0.0	0.7 ± 0.0	0.8 ± 0.0 *	0.7 ± 0.0
Liver/BW	30.4 ± 0.2	30.6 ± 0.3	30.8 ± 0.3	29.7 ± 0.3 *	31.0 ± 0.3	30.3 ± 0.3
Kidney/BW	5.3 ± 0.0	5.4 ± 0.1	5.6 ± 0.1 *	5.4 ± 0.1	5.7 ± 0.2	5.8 ± 0.0 *
Testes/BW	8.1 ± 0.1	8.3 ± 0.1	8.4 ± 0.1	9.1 ± 0.1 *	8.2 ± 0.5	8.4 ± 0.2

Data are expressed as mean +/- standard error of the mean of 15 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test.

Table 22. Organ Weights and Organ/Body Weight Ratios for 6-Month Rodents

6 Month	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High	Nickel
Spleen (mg)	938 ± 29	936 ± 39	959 ± 29	862 ± 14 *	1010 ± 28	1042 ± 16 *	901 ± 18
Thymus (mg)	378 ± 34	374 ± 17	423 ± 20	299 ± 23	335 ± 12	315 ± 14	274 ± 15 *
Liver (gm)	12.9 ± 0.2	12.6 ± 0.3	12.8 ± 0.2	11.5 ± 0.2 *	13.9 ± 0.2	12.5 ± 0.2	12.4 ± 0.2
Kidney (mg)	1128 ± 15	1111 ± 25	1144 ± 32	1007 ± 15 *	1220 ± 14 *	1130 ± 11	1112 ± 15
Testes (mg)	1548 ± 25	1579 ± 28	1545 ± 32	1557 ± 28	1610 ± 17 *	1552 ± 14	1544 ± 31
Spleen/BW	2.1 ± 0.1	2.2 ± 0.1	2.2 ± 0.1	2.1 ± 0.0	2.2 ± 0.1	2.74± 0.0 *	2.1 ± 0.0
Thymus/BW	0.8 ± 0.1	0.9 ± 0.0	1.0 ± 0.0	0.7 ± 0.1	0.7 ± 0.0	0.8 ± 0.1	0.6 ± 0.0 *
Liver/BW	29.3 ± 0.3	29.2 ± 0.3	29.1 ± 0.2	28.3 ± 0.3 *	30.0 ± 0.2	29.1 ± 0.2	28.9 ± 0.3
Kidney/BW	5.1 ± 0.1	5.1 ± 0.1	5.2 ± 0.1	5.0 ± 0.1 *	5.3 ± 0.1 *	5.3 ± 0.1 *	5.2 ± 0.1
Testes/BW	7.0 ± 0.1	7.3 ± 0.1	7.0 ± 0.1	7.7 ± 0.1 *	7.0 ± 0.1	7.3 ± 0.1 *	7.2 ± 0.1

Data are expressed as mean +/- standard error of the mean of 20 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test.

Table 23. Organ Weights and Organ/Body Weight Ratios for 12-Month Rodents

12 Month	Non-Surgical	Tantalum	DU-Low	DU-High
Spleen (mg)	1045 ± 22	990 ± 25	1015 ± 21	976 ± 24 *
Thymus (mg)	347 ± 34	334 ± 24	301 ± 21	284 ± 22
Liver (gm)	14.4 ± 0.3	15.2 ± 0.3	14.9 ± 0.2	13.5 ± 0.2 *
Kidney (mg)	1303 ± 19	1306 ± 24	1313 ± 17	1210 ± 18 *
Testes (mg)	1660 ± 23	1708 ± 19	1746 ± 28	1659 ± 19
Spleen/BW	2.1 ± 0.2	1.9 ± 0.1	1.9 ± 0.1	2.0 ± 0.2
Thymus/BW	0.7 ± 0.1	0.6 ± 0.1	0.6 ± 0.0	0.6 ± 0.0
Liver/BW	28.3 ± 0.4	29.3 ± 0.2	28.7 ± 0.3	28.0 ± 0.3
Kidney/BW	5.1 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	5.0 ± 0.1
Testes/BW	6.5 ± 0.1	6.6 ± 0.1	6.7 ± 0.1	6.9 ± 0.1 *

Data are expressed as mean +/- standard error of the mean of 10 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test.

Table 24. Organ Weights and Organ/Body Weight Ratios for 18-Month Rodents

18 Month	Non-Surgical	Tantalum	DU-Low	DU-High
Spleen (mg)	1701 ± 401	1242 ± 88	3119 ± 1431	1094 ± 35
Thymus (mg)	ND	ND	ND	ND
Liver (gm)	14.4 ± 0.3	14.4 ± 0.4	14.1 ± 0.6	12.8 ± 0.4 *
Kidney (mg)	1374 ± 23	1425 ± 19	1383 ± 25	1288 ± 26 *
Testes (mg)	1734 ± 70	1724 ± 73	1656 ± 75	1668 ± 90
Spleen/BW	3.6 ± 0.9	2.5 ± 0.2	6.9 ± 3.2	2.4 ± 0.1
Thymus/BW	ND	ND	ND	ND
Liver/BW	30.0 ± 0.8	29.2 ± 0.8	30.2 ± 1.2	27.4 ± 0.6 *
Kidney/BW	5.7 ± 0.1	5.8 ± 0.1	5.9 ± 0.1	5.5 ± 0.1
Testes/BW	7.2 ± 0.3	7.0 ± 0.3	7.1 ± 0.3	7.2 ± 0.4

Data are expressed as mean +/- standard error of the mean of 10 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test. ND is not determined.

Table 25. Organ Weights and Organ/Body Weight Ratios for 24-Month Rodents

24 Month	Non-Surgical	Tantalum	DU-Low	DU-High
Spleen (mg)	4400 ± 1609	1612 ± 337	2608 ± 1219	1488 ± 174
Thymus (mg)	ND	ND	ND	ND
Liver (gm)	15.2 ± 1.2	14.7 ± 0.8	15.3 ± 2.1	13.2 ± 0.9
Kidney (mg)	1494 ± 41	1410 ± 67	1519 ± 38	1463 ± 94
Testes (mg)	1480 ± 151	1549 ± 119	1505 ± 130	1455 ± 90
Spleen/BW	10.2 ± 3.6	3.5 ± 0.7	5.5 ± 2.6	3.5 ± 0.4
Thymus/BW	ND	ND	ND	ND
Liver/BW	33.8 ± 2.6	31.7 ± 1.4	32.9 ± 4.4	30.5 ± 2.3
Kidney/BW	6.7 ± 0.3	6.1 ± 0.3	6.6 ± 0.1	6.8 ± 0.5
Testes/BW	6.5 ± 0.6	6.8 ± 0.5	6.5 ± 0.6	6.7 ± 0.4

Data are expressed as mean +/- standard error of the mean of 16 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test. ND is not determined.

Table 26. Serum and urine mutagenicity data for 6- and 12-month rodents

Time (months)	Experimental Group	Mutagenicity (revertants/ul sample)
	Serum	
6 month	Non-Surgical	0.171
	Tantalum	0.188
	DU-Low	0.154
	DU-High	0.129
	WA-Low	0.133
	WA-High	0.117
	Nickel	0.165
12 month	Non-Surgical	0.171
	Tantalum	0.188
	DU-Low	0.154
	DU-High	0.129
	Urine	
6 month	Non-Surgical	29.42 ± 10.08
	Tantalum	27.85 ± 11.80
	DU-Low	45.83 ± 10.78
	DU-High	115.18 ± 15.35
	WA-Low	58.04 ± 12.31
	WA-High	94.37 ± 13.95
	Nickel	44.75 ± 10.63
12 month	Non-Surgical	35.92 ± 8.14
	Tantalum	33.57 ± 9.60
	DU-Low	83.28 ± 10.34
	DU-High	257.53 ± 32.81

Table 27. Immune Organ Cellularities for 1-Month Rodents

1 Month	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
Spleen Cellularity (10e8 cells/g tissue)	25.9 ± 1.2	21.9 ± 1.1	24.7 ± 1.4	24.1 ± 1.5	19.3 ± 0.9 *	17.4 ± 1.0 *
Thymus Cellularity (10e8 cells/g tissue)	32.2 ± 1.3	22.6 ± 1.4	21.4± 1.7 *	27.4 ± 2.3	22.6 ± 1.1 *	22.4 ± 1.1 *
Bone Marrow Cellularity (10e7 cells/femur)	9.3 ± 0.6	11.2 ± 1.2	8.8 ± 0.5	8.2 ± 0.6	10.0 ± 0.5	9.0 ± 0.4

Data are expressed as mean +/- standard error of the mean of 15 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test.

Table 28. Immune Organ Cellularities for 3-Month Rodents

3 Month	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
Spleen Cellularity (10e8 cells/g tissue)	24.2 ± 1.5	22.7 ± 1.2	20.5 ± 0.8 *	21.8 ± 1.0	20.2 ± 1.0 *	21.4 ± 1.1
Thymus Cellularity (10e8 cells/g tissue)	19.3 ± 0.7	23.1 ± 1.3	21.6± 1.7	25.2 ± 2.2 *	18.1 ± 1.0	22.9 ± 1.6
Bone Marrow Cellularity (10e7 cells/femur)	10.2 ± 0.6	9.5 ± 0.7	8.3 ± 0.4 *	8.0 ± 0.4 *	8.6 ± 0.4 *	11.5 ± 0.5

Data are expressed as mean +/- standard error of the mean of 15 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test.

Table 29. Immune Organ Cellularities for 6-Month Rodents

6 Month	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
Spleen Cellularity (10e8 cells/g tissue)	33.2 ± 1.4	29.9 ± 1.6	22.0 ± 1.2 *	26.9 ± 1.7 *	31.0 ± 1.6	27.2 ± 1.3 *
Thymus Cellularity (10e8 cells/g tissue)	10.6 ± 1.0	12.9 ± 1.4	7.1 ± 0.7 *	15.3 ± 1.2 *	8.4 ± 0.4	11.2 ± 0.5
Bone Marrow Cellularity (10e7 cells/femur)	13.0 ± 0.6	12.3 ± 0.5	7.8 ± 0.4 *	11.5 ± 0.5	11.6 ± 0.9	13.4 ± 0.8

Data are expressed as mean +/- standard error of the mean of 15 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test.

Table 30. Immune Organ Cellularities for 12-Month Rodents

12 Month	Non-Surgical	Tantalum	DU-Low	DU-High
Spleen Cellularity (10e8 cells/g tissue)	29.7 ± 1.2	31.3 ± 1.8	31.2 ± 1.4	27.7 ± 1.7
Thymus Cellularity (10e8 cells/g tissue)	8.5 ± 1.0	6.6 ± 1.0	4.6 ± 0.7 *	8.3 ± 0.7
Bone Marrow Cellularity (10e7 cells/femur)	14.8 ± 1.2	13.6 ± 0.7	12.7 ± 1.0	10.7 ± 0.7 *

Data are expressed as mean +/- standard error of the mean of 15 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test.

Table 31. Natural Killer Cell Activity

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
1 Month	17.1 ± 0.9	11.4 ± 2.0	7.6 ± 1.0 *	11.6 ± 3.8	10.2 ± 1.0 *	7.5 ± 1.2 *
3 Month	19.1 ± 2.6	16.9 ± 1.4	14.3 ± 1.9	9.0 ± 2.7 *	5.8 ± 2.0 *	8.2 ± 3.0 *
6 Month	ND	ND	ND	ND	ND	ND
12 Month	ND	ND	ND	ND	ND	ND

Data expressed as the mean +/- the standard error of the mean of 15 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test. ND is not detected.

Table 32. Cytotoxic T-Lymphocyte Activity

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
1 Month	31.2 ± 5.8	28.4 ± 5.7	21.6 ± 1.7	31.0 ± 6.6	25.1 ± 1.4	21.2 ± 1.8
3 Month	37.3 ± 2.5	20.1 ± 0.8	44.8 ± 1.9 *	44.8 ± 4.4	42.7 ± 5.5	30.0 ± 2.1 *
6 Month	37.8 ± 6.4	33.8 ± 1.0	13.5 ± 0.8 *	17.7 ± 0.7 *	20.5 ± 4.0 *	22.2 ± 3.1 *
12 Month	29.0 ± 1.8	18.2 ± 1.1	36.1 ± 4.4	34.6 ± 5.2	ND	ND

Data expressed as the mean +/- the standard error of the mean of 15 replicates. * represents a significant difference from control at $P<0.05$ using Students t-test. ND is not determined.

Table 33. Antibody Plaque-Forming Cell Activity

	Non-Surgical	Tantalum	DU-Low	DU-High	WA-Low	WA-High
1 Month	1.52 ± 0.32	3.55 ± 0.5	3.33 ± 0.35 *	1.87 ± 0.18	2.26 ± 0.55	1.84 ± 0.21
3 Month	1.23 ± 0.10	3.24 ± 0.60	1.58 ± 0.12 *	2.59 ± 0.92	0.87 ± 0.11 *	5.22 ± 0.89 *
6 Month	4.76 ± 0.62	3.02 ± 0.70	2.33 ± 0.54 *	1.16 ± 0.11 *	1.25 ± 0.29 *	ND
12 Month	3.97 ± 0.64	0.87 ± 0.20	0.74 ± 0.12 *	2.46 ± 0.35	ND	ND

Data expressed as the mean +/- the standard error of the mean of 15 replicates and represent the number of plaques (x 10e5) formed per spleen. * represents a significant difference from control
at $P<0.05$ using Students t-test. ND is not determined.